

Survival Analysis of High-Intensity Focused Ultrasound Therapy Versus Radiofrequency Ablation in the Treatment of Recurrent Hepatocellular Carcinoma

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Objective: To evaluate our preliminary experience of high-intensity focused ultrasound (HIFU) for the treatment of recurrent hepatocellular carcinoma (HCC).

Background: HIFU is a new thermal ablative therapy for HCC. Whether it incurs survival benefit similar to that of radiofrequency ablation (RFA) remains uncertain.

Methods: Clinicopathological data of 27 patients who received HIFU ablation and 76 patients who received RFA for recurrent HCC from October 2006 to October 2009 were reviewed. Survival outcomes between the 2 groups were compared using the log-rank test. A value of $P < 0.05$ was considered significant.

Results: The median follow-up was 27.9 months. There was no difference in tumor size (HIFU, 1.7 cm; RFA, 1.8 cm; $P = 0.28$) between the 2 groups. Procedure-related morbidity rate was 7.4% in the HIFU group and 6.5% in the RFA group ($P = 1.00$). Skin burn and pleural effusion were the 2 morbidities associated with HIFU. There was no hospital mortality in the HIFU group, whereas 2 deaths occurred in the RFA group. The 1-, 2-, and 3-year disease-free survival rates were 37.0%, 25.9%, and 18.5%, respectively, for the HIFU group, and 48.6%, 32.1%, and 26.5%, respectively for the RFA group ($P = 0.61$). The 1-, 2-, and 3-year overall survival rates were 96.3%, 81.5%, and 69.8%, respectively, for the HIFU group, and 92.1%, 76.1%, and 64.2%, respectively, for the RFA group ($P = 0.19$).

Conclusions: Our preliminary experience in using HIFU for recurrent HCC is promising. Further studies are needed to explore its treatment value for primary HCC.

Keywords: hepatocellular carcinoma, high-intensity focused ultrasound, radiofrequency ablation, recurrence, recurrent HCC

(*Ann Surg* 2013;257: 686–692)

Hepatocellular carcinoma (HCC) is the fifth most common malignancy in the world. Although it is a common disease in Eastern countries due to the prevalence of chronic hepatitis B infection, its incidence in Western countries has been rising in recent years.^{1,2} Hepatic resection forms the cornerstone for surgical management of HCC. However, postresection tumor recurrence is common with a 5-year recurrence rate of over 50%.³ Salvage treatment for recurrent HCC poses several challenges, especially when tumor recurrence occurs in a small and cirrhotic remnant liver. Other factors such as

inadequate liver function, adhesions due to previous operations, and tumor location in the vicinity of major hepatic vessels or bile ducts in the liver remnant are major limitations to further resections and hence alternative treatments are being sought.

The advent of local ablative therapy revolutionized the treatment algorithm for HCC over the last decade.⁴ Recently, high-intensity focused ultrasound (HIFU) ablation has emerged as a new form of local ablative therapy.^{5,6} This innovative treatment entails delivery of a high-intensity ultrasound beam from an extracorporeal energy source into a targeted area causing hyperthermia and coagulation necrosis of tumor cells. Our center has applied this treatment to patients with recurrent or advanced HCC since its inception in 2006. The aim of this study was to evaluate the postoperative and oncologic outcome of this treatment in comparison with radiofrequency ablation (RFA) in the management of recurrent HCC.

PATIENTS AND METHODS

From October 2006 to October 2009, 103 patients with recurrent HCC underwent either HIFU ablation or RFA at our hospital. All selected patients with tumor recurrence received either hepatectomy or RFA as the primary treatment for the primary HCC and they were the focus of this study. All clinicopathological data were collected prospectively by a designated research officer. Survival data were updated after each follow-up visit according to our tumor surveillance protocol.

Treatment Algorithm of Recurrent HCC After Hepatectomy

The selection criteria for local ablative therapy for recurrent HCC were Child-Pugh class A or selected patients with Child-Pugh class B cirrhosis, unresectable tumor, tumor size of 5 cm or more, and fewer than 3 tumor nodules (Fig. 1). Salvage liver transplantation was not offered due to the local policy of allocating deceased-donor liver grafts to patients with Child-Pugh class C cirrhosis only. Exclusion criteria for local ablative therapy included portal vein invasion by tumor and/or presence of distant metastasis. The choice of treatment for recurrent HCC depended on the sonographic feature of the tumor, its location in relation to adjacent organs, and patient consent. HIFU therapy was offered when tumor was visualized on real-time diagnostic ultrasonography in the HIFU system, especially for periductal tumor, which is susceptible to bile duct injury with RFA. On the other hand, patients with sonographically undetectable lesion and/or tumor located adjacent to bowels were selected for RFA. If the tumor was eligible for both HIFU ablation and RFA, the decision for treatment depended on the agreement between the patient and the surgeon after a thorough discussion of the pros and cons of both treatment options.

Preparation for HIFU Treatment

The patient was fasted for 6 hours before treatment. Routine blood sampling was performed for renal and liver functions, hemoglobin level, platelet count, white cell count, and clotting

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Disclosure: None of the authors has any financial interests or any conflicts of interest with regard to the manuscript. No additional funding support was involved. The authors declare no conflicts of interest.

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ISSN: 0003-4932/13/25704-0686

DOI: 10.1097/SLA.0b013e3182822c02

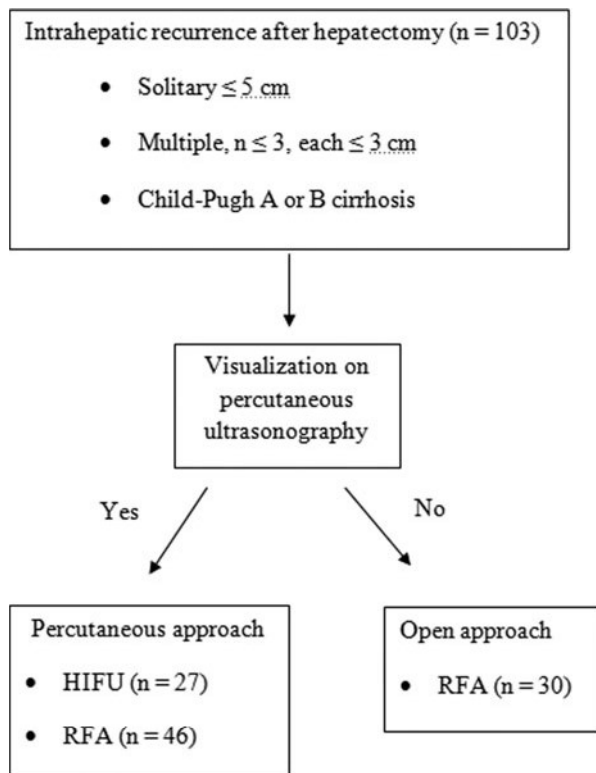


FIGURE 1. Treatment algorithm for recurrent HCC after hepatectomy.

profile. A chest radiograph and an echocardiogram were performed to assess the cardiorespiratory fitness for general anesthesia. The patient was then assessed by an anesthetist for preoperative risk assessment. An informed consent was obtained after a detailed explanation of the treatment benefits and potential complications of the procedure. In the morning of the treatment, the skin was cleansed by degassed water and a negative pressure aspirator was used to degas the skin to reduce its dampening effect on ultrasonic waves.

HIFU Therapy

The HIFU machine (JC model Focused Ultrasound Tumor Therapeutic System, Chongqing Haifu (HIFU) Technology, Chongqing, China) was installed in our hospital in 2006. Since then, we have offered HIFU therapy to almost 100 patients with recurrent or advanced HCC. All patients receiving HIFU therapy needed to be anesthetized for the procedure as it was mandatory to control the breathing movement to minimize the degree of displacement of the liver by the diaphragm and for adequate pain control. The patient was then placed in the center of the water reservoir and turned to a right lateral position if the tumor was located in the right liver, or to a prone position if the tumor was located in the left liver. The treatment head, which comprised a transducer, lied at the center of the water reservoir. It is able to move in 3 orthogonal planes along the *x*, *y*, and *z* axes, and rotate around 90° to enable tumor localization. The frequency of the transducer was 0.8 MHz with a focal length ranging from 100 to 160 mm. Tumor location was then confirmed by real-time two-dimensional liver ultrasonography and the treatment pathway was determined. It was important to ensure that no adjacent organ, such as the large bowels or gallbladder, lied within the treatment pathway to prevent collateral damage to these organs. Artificial pleural effu-

sion and ascites were created if deemed necessary for improvement in the efficiency of ultrasound transmission. Treatment powers ranging from 230 to 466 watts were adopted. During the treatment, special attention was paid to possible changes of the tumor location caused by the diaphragmatic movement so as to avoid overshooting or undershooting of the tumor. A rise in the temperature on the skin surface may also occur and regular monitoring of skin changes was crucial to prevent thermal injury.

Post-HIFU Preparation

The patient was awakened after reversal of general anesthesia and vital signs, including body temperature, blood pressure, heart rate, and oxygen saturation, were closely monitored. Abdominal examination was routinely performed to assess for any peritoneal sign due to peritoneal irritation or ruptured viscera. The overlying skin of the treated area was assessed for physical signs of thermal injury. Blood sampling for renal and liver function was performed. Full diet was resumed as soon as the patient regained full consciousness and was free from abdominal complaints.

Follow-up Strategy After HIFU Treatment of Recurrent Tumor

Magnetic resonance imaging (MRI) was performed 1 month after the treatment to assess for completeness of tumor ablation. Complete ablation was defined as the absence of hyperintense signal on T2-weighted imaging and contrast enhancement within the ablated tumor area (Fig. 2). The presence of T2 hyperintense signal and/or contrast-enhanced signal within the original tumor area was defined as incomplete ablation. Surveillance for tumor recurrence was performed at a 3-month interval using MRI and measurement of serum alpha-fetoprotein level. Tumor recurrence was defined as new hypointense signals on T1-weighted images and hyperintense signal on T2-weighted images with arterial enhancement and portal venous washout on contrast films.

Follow-up Strategy After RFA Treatment of Recurrent Tumor

Computed tomography (CT) or MRI was performed 1 month after RFA treatment to confirm complete tumor clearance. Complete ablation was defined as the absence of contrast-enhanced signal within the ablated tumor area. Incomplete ablation was defined as the presence of contrast-enhanced signal within the ablated tumor area. Surveillance strategy for tumor recurrence is identical with that of HIFU treatment. Intrahepatic recurrence was defined as a new lesion with arterial enhancement and portal venous washout on contrast-enhanced CT scan or MRI scan.

Data Analysis

Continuous variables were expressed as median (interquartile range) and compared using the Mann-Whitney *U* test. Categorical variables were compared with the χ^2 test or Fisher exact test where appropriate. The overall and tumor-free survival rates of the 2 study groups were estimated using the Kaplan-Meier method and compared using the log-rank test. Overall survival was defined as the period from the date of treatment for first tumor recurrence to the date of death related to all causes. Disease-free survival was defined as the period between the date of treatment of first tumor recurrence to the date of second tumor recurrence or death (excluding hospital mortality). Univariate analysis for the identification of prognostic factors for disease-free survival after treatment of recurrent HCC was performed by comparing the median survival rates using the Mann-Whitney *U* test. Significant prognostic factors identified by univariate analysis were entered into a Cox proportional hazards model for multivariable

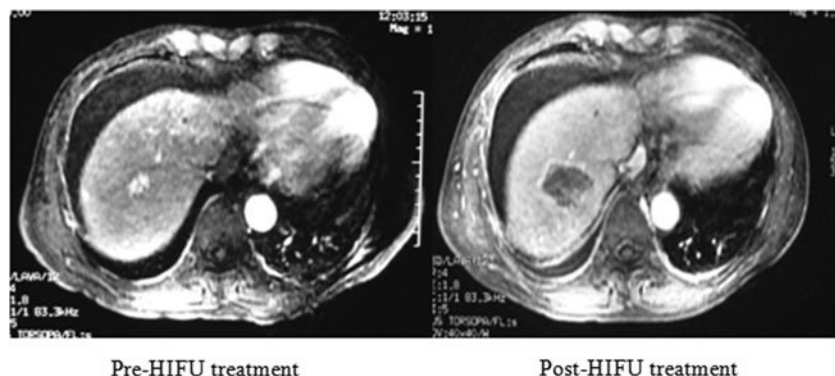


FIGURE 2. HIFU therapy for a 68-year-old patient with tumor recurrence in segment 8 of the liver before and after treatment. Tumor ablation marked by hypointense signal on MRI image.

analysis. A value of $P < 0.05$ was considered to be statistically significant. Statistical analysis was performed using the SPSS 16.0 computer software (SPSS, Chicago, IL, USA).

RESULTS

Table 1 lists the patient characteristics of the 2 groups. Twenty-seven patients received HIFU ablation and 76 patients received RFA. The median age in the HIFU group and in the RFA group was 63 and 62 years, respectively. Medical comorbidities were observed in 66.7% of the patients receiving HIFU treatment and 64.5% of the patients receiving RFA ($P = 0.97$). The incidence of hepatitis B surface antigen positivity was similar between the 2 groups. The RFA group had significantly more patients with Child-Pugh B cirrhosis. There was no significant difference in primary tumor characteristics between the 2 groups in terms of tumor size, tumor number, serum alpha-fetoprotein level, and tumor staging (Table 2). Table 3 shows the pathological features of the recurrent HCC. The recurrent tumor size in patients receiving HIFU ablation and RFA was 17 mm (9–50 mm) and 18 mm (7–49 mm), respectively ($P = 0.28$), and the serum alpha-fetoprotein level was 8 ng/mL (2–3951 ng/mL) and 17 ng/mL (2–8090 ng/mL), respectively ($P = 0.25$). Also 80.3% of the patients in the RFA group and 81.5% of the patients in the HIFU group had single tumor recurrence ($P = 0.50$). Complete tumor ablation rates were above 80% in both the treatment groups. The median HIFU exposure time was 26 minutes and the total operating time was 151 minutes (24–360 minutes). The median amount of energy delivered was 574 kilojoules (612–1994 kilojoules). Among patients receiving RFA, 46 patients underwent the percutaneous approach, whereas 27 patients underwent the open approach and 3 patients underwent the laparoscopic approach. The median procedure time was 151 minutes (24–360 minutes) and it did not differ significantly from the HIFU procedure time ($P = 0.53$). The procedure-related morbidity rate was 7.4% in the HIFU group and 22.4% in the RFA group ($P = 0.44$). After excluding cases of open and laparoscopic RFA, the procedure-related morbidity rate of patients receiving percutaneous RFA was 6.5%, a rate comparable with that of HIFU ablation ($P = 1.00$). The causes of procedure-related morbidities in the 2 groups are listed in Table 4. There was no hospital mortality in the HIFU group, whereas 2 postoperative deaths occurred in the RFA group.

Procedure-Related Morbidity After HIFU Treatment

Skin complication developed in a 74-year-old man with a medical history of diabetes mellitus. He had a recurrent tumor measuring $1.5 \times 1.6 \times 1.7$ cm in segment 2 of the liver adjacent to the left hepatic vein after resection of the primary tumor 5 years before. HIFU therapy was commenced at a power of 450 watts and an energy output of 1260 kilojoules. The treatment lasted for 45 minutes. At the end of the procedure, an area of 12.0×1.0 cm second-degree skin burn was

TABLE 1. Patient Characteristics in the 2 Groups

	HIFU (n = 27)	RFA (n = 76)	P
Age (years)	63 (44–75)	62 (28–84)	0.95
Sex (M:F)	25:2	55:21	0.03
HBsAg	21 (77.8%)	64 (84.2%)	0.11
Comorbid illness	18 (66.7%)	49 (64.5%)	0.97
Cardiovascular disease	1 (3.7%)	6 (7.9%)	
Hypertension	10 (37%)	21 (27.6%)	
Pulmonary disease	4 (14.8%)	7 (9.2%)	
Diabetes mellitus	3 (11.1%)	15 (19.7%)	
Previous hepatectomy	17 (63%)	36 (47.7%)	0.18
Child-Pugh class			
A	24 (88.9%)	51 (67.1%)	0.09
B	3 (11.1%)	25 (32.9%)	0.03
Serum bilirubin ($\mu\text{mol/L}$)	16 (7–42)	13 (4–61)	0.29
AST (U/L)	45 (19–308)	36.5 (17–96)	0.05
Albumin (g/L)	39 (24–45)	41 (25–47)	0.24
Platelet count ($10^9/\text{L}$)	103 (46–235)	128.5 (17–291)	0.65
Urea (mmol/L)	5.3 (3.4–22.9)	5.45 (2.9–10.6)	0.92
Creatinine ($\mu\text{mol/L}$)	88 (44–380)	82.5 (49–135)	0.09
Serum AFP (ng/mL)	8 (2–3951)	17 (2–8090)	0.25

AFP indicates alpha-fetoprotein; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen.

TABLE 2. Tumor Characteristics of the Primary HCC

	HIFU (n = 27)	RFA (n = 76)	P
Tumor size (cm)	3.50 (1.5–11.0)	3.45 (1.0–12.1)	0.907
Number of tumor nodules	1 (1–multiple)	1 (1–multiple)	0.637
Serum AFP (ng/mL)	31.5 (3–9838)	63 (2–388,800)	0.283
AJCC staging (sixth edition)			0.82
I	17	45	
II	6	16	
IIa	3	6	
IIb	0	2	
Unclassified	1	7	

AFP indicates alpha-fetoprotein.

found in the epigastrium. Daily wound dressing was applied and the patient was discharged 4 days after the procedure. This dermal complication eventually recovered after regular wound dressing without any need for wound reconstruction.

The second patient was a 73-year-old hepatitis C carrier who received ultrasound-guided percutaneous RFA for a segment 7 HCC 2 years before HIFU treatment. Two sites of tumor recurrences anterior to the previous RFA site were detected by MRI. HIFU treatment was

TABLE 3. Tumor Characteristics of Recurrent HCC and Patterns of Second Recurrence After Treatments

	HIFU (n = 27)	RFA (n = 76)	P
Recurrent tumor size (cm)	1.7 (0.9–5.0)	1.8 (0.7–4.9)	0.28
No. patients with solitary tumor recurrence (%)	22 (81.5%)	61 (80.3%)	0.50
Serum AFP on tumor recurrence (ng/mL)	8 (2–3951)	17 (2–8090)	0.25
Time to tumor recurrence after treatment of primary HCC (months)	14.92 (1.05–105.13)	30.36 (0.99–176.93)	0.34
Patterns of second tumor recurrence after treatment of first recurrence (%)			0.29
Intrahepatic	15 (55.6%)	28 (37.8%)	
Extrahepatic	0	5 (6.8%)	
Both	2 (7.4%)	6 (8.1%)	

AFP indicates alpha-fetoprotein.

TABLE 4. Short-Term Outcomes in Patients of the 2 Groups

	HIFU (n = 27)	RFA (n = 76)	P
Complete ablation rate	23 (85.2%)	65 (87.8%)	0.99
Procedure-related morbidity			0.06
Pneumonia	0	1	
Pleural effusion	1	5	
Wound complications	0	4	
Cardiac complications	0	3	
Liver abscess	0	2	
Acute cholecystitis	0	1	
Ascites	0	1	
Rupture of the diaphragm	0	1	
Chest wall and abdominal pain	0	2	
Ileus	0	1	
Second-degree skin burn	1	0	
Others	0	4	
Total	2 (7.4%)	25 (22.4%)	
Hospital stay (days)	4 (2–12)	4 (2–35)	0.08
Hospital mortality rate	0%	2.6%	0.44

applied to these 2 lesions with the power at 415 watts and a total energy output of 791 kilojoules. The treatment session lasted for 32 minutes. The patient developed pyrexia and right pleural effusion the next day after the procedure. Blood culture did not grow any causative organism. Broad-spectrum carbapenem-group antibiotic was commenced and the pleural effusion was resolved spontaneously on serial chest radiography.

Long-Term Outcomes of Patients Receiving HIFU and RFA Treatments

The median follow-up period for the HIFU group and the RFA group was 30.3 and 24.6 months, respectively ($P = 0.31$). Thirty-five patients in the HIFU group and 10 patients in the RFA group remained recurrence free at the time of analysis. Intrahepatic recurrence remained to be the most common pattern of recurrence in both the treatment groups (HIFU: $n = 15$; RFA: $n = 28$). The 1-, 2-, and 3-year disease-free survival rates for the HIFU group were 37.0%, 25.9%, and 18.5%, respectively, and for the RFA group, they were 48.6%, 32.1%, and 26.5%, respectively ($P = 0.61$) (Fig. 3). The 1-, 2-, and 3-year overall survival rates for the HIFU group were 96.3%, 81.5%, and 69.8%, respectively, and for the RFA group, they were 92.1%, 76.1%, and 64.2%, respectively ($P = 0.38$) (Fig. 4). No significant difference in disease-free survival or overall survival was found between the HIFU group and RFA patients with sonographically de-

tectable tumors, who had 1-, 2-, and 3-year disease-free survival rates of 45.7%, 32.6%, and 32.6%, respectively ($P = 0.51$) (Fig. 5A) and overall survival rates of 93.5%, 78.3%, and 71.2%, respectively ($P = 0.88$) (Fig. 5B).

After adjustment of the Child-Pugh grading that analyzed patients with Child-Pugh A cirrhosis, the 1-, 2-, and 3-year disease-free survival rates were 37.5%, 29.2%, and 20.8%, respectively, in the HIFU group and 52.9%, 36.9%, and 31.8%, respectively, in the RFA group ($P = 0.61$), whereas the 1-, 2-, and 3-year overall survival rates were 100%, 83.3%, and 70.2%, respectively, in the HIFU group and 96.1%, 80.1%, and 64.6%, respectively, in the RFA group ($P = 0.17$).

Univariate analysis of the 9 clinicopathological factors showed that tumor recurrence within 12 months after treatment of primary HCC and second tumor recurrence within 12 months after treatment of first recurrence of HCC were unfavorable prognostic factors for disease-free survival (Table 5). When these 2 factors were entered into multivariable analysis, only tumor recurrence within 12 months after treatment of primary HCC remained to be an independent poor prognostic factor (hazard ratio, 4.237; 95% confidence interval, 2.616–6.862; $P < 0.001$) for disease-free survival.

DISCUSSION

The concept of utilizing high-energy ultrasound beam to induce hyperthermia and tissue damage was first proposed by the Fry

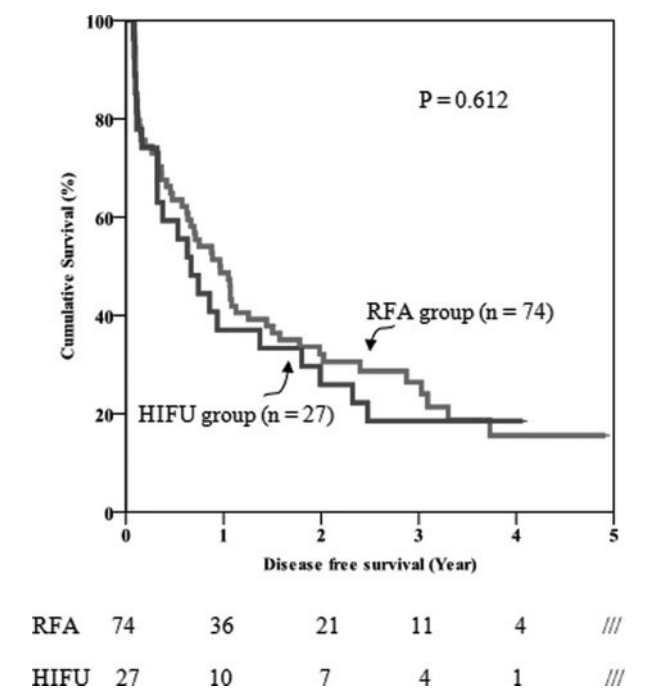


FIGURE 3. Disease-free survival of patients receiving HIFU versus RFA for recurrent HCC.

brothers in Illinois in the early 1950s when they experimented this technology in the treatment of Parkinson disease.⁷ It was until the 1990s that the interest in applying HIFU therapy in the treatment of solid tumors was aroused again. The tumor destructive effect of HIFU therapy has been confirmed in both in vitro and in vivo models,^{8–10} but data on its clinical efficacy for the treatment of HCC is still lacking. Our preliminary experience in the application of HIFU for HCC has been recently published.¹¹ Since its inception in our center in 2006, we started to offer this treatment to patients with recurrent HCC that is amenable to locoregional treatment. The rationale for this treatment policy relates to the intrinsic advantages of HIFU therapy over other local ablative therapies. First, HIFU ablation is an extracorporeal conformal therapy, meaning no surgical exposure is required to deliver the energy source to the targeted lesion. This is particularly appealing to patients with postresection tumor recurrence as a second operation is avoided. Second, the concern of tumor cell seeding along the needle tract, a phenomenon that could potentially occur with other forms of local ablative therapy, is no longer valid. Third, the avoidance of tumor puncturing by the energy probe eliminates the risk of tumor cell dissemination into the circulation, especially for tumors located in the vicinity of major vessels.¹² Similar to RFA, HIFU therapy induces hyperthermia up to 60–100°C at the targeted area. Within this range of temperature, water within the body tissue starts to vaporize followed by microbubble formation. Cavitation then ensues¹³ and cell death occurs through the process of coagulation necrosis. With this technology, we attained a complete tumor ablation rate of over 80%, which is comparable with that of RFA. Tumor ablation is signified by increased echogenicity, a phenomenon called gray-scale changes, and is dependent on tumor visualization on ultrasound imaging. The overall ablation rate from other studies varies from 28% to 72%.^{14–16} Complete tumor ablation could be difficult when the tumor is situated in difficult locations such as segment 7 or in the subcapsular area. Given that fluid is an ideal medium for propagation of ultrasonic waves, the use of artificial ascites or pleural

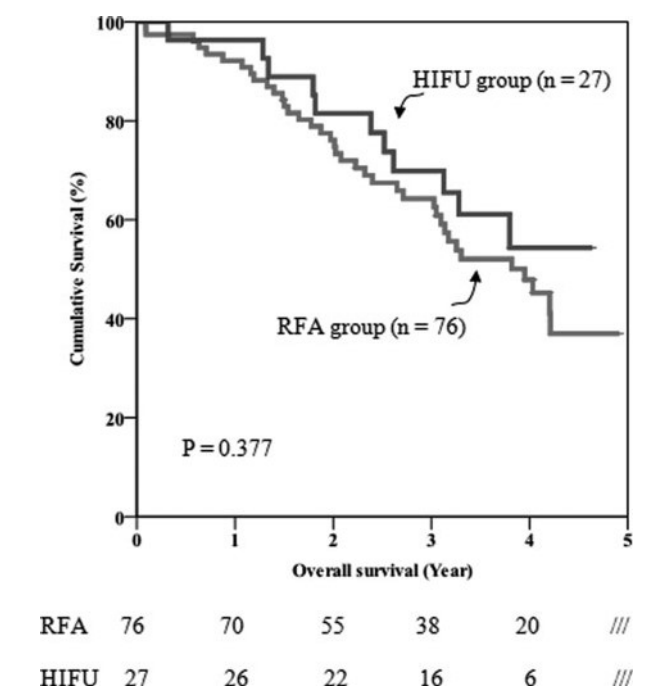


FIGURE 4. Overall survival of patients receiving HIFU versus RFA for recurrent HCC.

effusion could improve the acoustic pathway so as to facilitate tumor identification and destruction.¹⁷

To our knowledge, this study is the first that evaluates the treatment efficacy of HIFU therapy in comparison with that of RFA. Our study demonstrated that HIFU therapy is a safe and feasible treatment modality for recurrent HCC with an acceptably low morbidity rate. The survival outcome of patients receiving HIFU therapy seemed to be comparable with that of patients receiving RFA, and corroborated the survival outcomes from other series.^{14,15,18} To reduce the confounding effect of different sorts of tumor biology that might influence the prognosis of patients in the 2 treatment groups, further survival analysis stratifying tumors according to their sonographic visibility and the severity of cirrhosis continued to show that patients with HIFU treatment had prognosis similar to those with RFA. The univariate analysis of the present study ascertained that the choice of treatment, be it HIFU or RFA, had similar prognostic influence on survival outcomes. Nonetheless, a small sample size and a non-randomized selection policy are the major weaknesses of the study and a prospective clinical trial is needed to evaluate the role of HIFU therapy in the treatment of HCC.

Early tumor recurrence after treatment of primary HCC is a poor prognostic factor for long-term survival and is thought to be related to intrahepatic metastasis rather than multicentric occurrence. Our study illustrated that only a small proportion of patients could achieve long-term disease-free survival despite the use of ablative therapy and the prognosis seemed to be unaltered regardless of the choice of treatment. Future research should therefore focus on the development of adjuvant treatment to improve the treatment outcome for primary HCC. The use of antiviral therapy after hepatic resection for hepatitis B carriers¹⁹ and the use of adjuvant molecular targeted therapy, such as sorafenib,²⁰ may offer the best hope to improve the curative rate of hepatic resection.

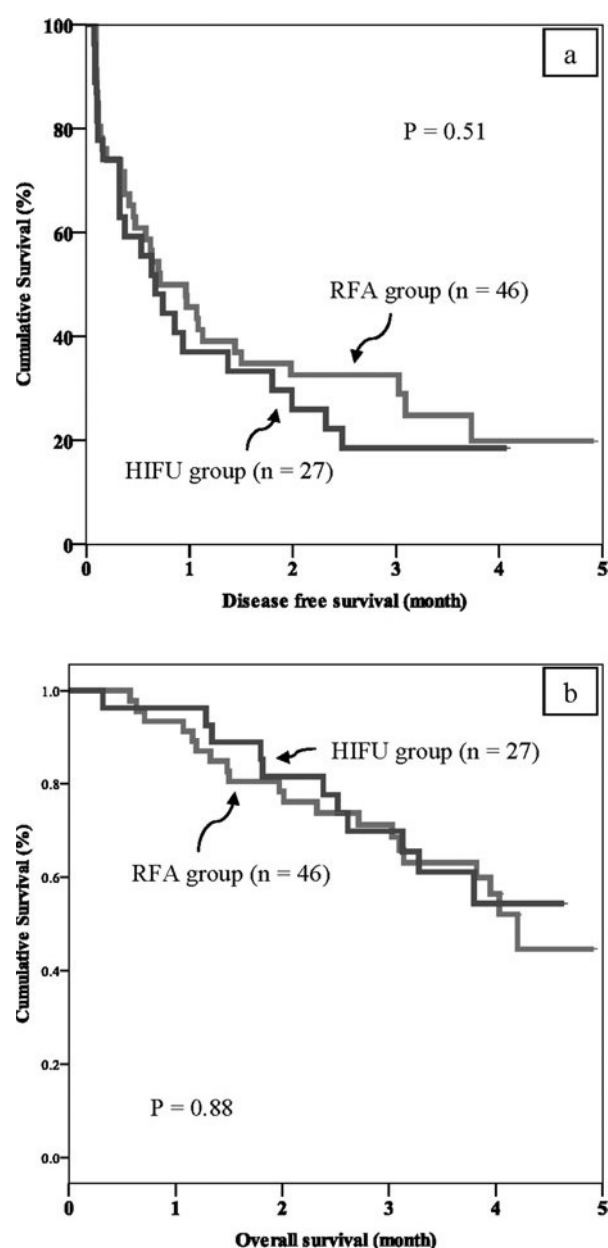


FIGURE 5. Survival outcomes of patients with sonographically detectable tumors: A, disease-free survival, B, overall survival.

CONCLUSIONS

From a surgeon's point of view, it is essential to be fully aware of the future development of local ablative therapy because the choice of surgical versus nonsurgical treatment could then be rationalized for our patients with postresection tumor recurrence, which is a frequent phenomenon encountered in clinical practice. The future development of an intracavitary device that could be employed in laparotomy or laparoscopy could potentially become a useful option in treating liver tumors in difficult locations.²¹ In fact, such device has already become available in the treatment of prostate diseases through the transrectal approach.^{22,23} On the other hand, the noninvasiveness of HIFU therapy could render it an ideal bridging therapy for patients with HCC who are wait-listed for liver transplantation. With accu-

TABLE 5. Univariate Analysis for Disease-Free Survival of 103 Patients With Recurrent HCC

	Median Survival (months)	P
Median age (years)		0.70
≤62 (n = 52)	8.53	
>62 (n = 49)	10.63	
HBsAg positivity		0.84
Yes (n = 89)	10.63	
No (n = 12)	4.40	
Primary tumor size (cm)		0.50
≤5 (n = 80)	10.53	
>5 (n = 21)	7.97	
Serum AFP (ng/mL) before primary treatment		0.49
≤400 (n = 75)	11.23	
>400 (n = 26)	4.40	
Time to first recurrence (months)		<0.0001
≤12 (n = 33)	3.20	
>12 (n = 68)	18.03	
Serum AFP (ng/mL) on second recurrence		0.19
≤400 (n = 90)	10.53	
>400 (n = 11)	4.40	
Child-Pugh classification		0.13
A (n = 75)	11.57	
B (n = 26)	7.47	
Choice of treatment for recurrent HCC		0.60
HIFU treatment (n = 27)	8.00	
RFA treatment (n = 74)	11.57	
Time to second recurrence (months)		<0.0001
≤12 (n = 55)	3.83	
>12 (n = 46)	34.50	

AFP indicates alpha-fetoprotein; HBsAg, hepatitis B surface antigen.

mulating experience in the clinical application of HIFU for recurrent HCC, we anticipate to witness an extension of its role to the treatment of other liver tumors in the near future.

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